Impact of stochastically generated heterogeneity in hazard rates on individually randomized vaccine efficacy trials

Title: Impact of stochastically generated heterogeneity in hazard rates on individually randomized vaccine efficacy trials

Running head: Impact of heterogeneous hazard rates

Word count: 1760

Authors: Rebecca Kahn[1], Matt Hitchings[1], Steven Bellan[2], Marc Lipsitch[1,3]

[1]Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America

[2]Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, Georgia, United States of America

[3]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America

Corresponding author:

Rebecca Kahn

Center for Communicable Disease Dynamics

Department of Epidemiology

Harvard T.H. Chan School of Public Health

677 Huntington Avenue

Boston, MA 02115

617-432-7955

rek160@mail.harvard.edu

Funding: This work was supported by Award Number U54GM088558 from the National Institute of General Medical Sciences. S.E.B. was supported by a National Institute of Allergy and Infectious Diseases K01 award (K01AI125830). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abstract

Background/Aims: Network structure and individuals' level of exposure to a pathogen can impact results from efficacy evaluation studies of interventions against infectious diseases. Heterogeneity in infection risk can cause randomized groups to increasingly differ as a trial progresses and as more high risk individuals become infected (described in prior work as the "frailty" phenomenon). Here we show the impact this phenomenon can have on an individually randomized trial of a leaky vaccine in which all participants are exchangeable *a priori.*

Methods: We model a vaccine trial by generating a network of individuals grouped into communities, which are connected to a larger main population. We then simulate an epidemic, deterministically and with time-varying transmission rates in the main population, and stochastically in the communities. The disease natural history follows a Susceptible-Exposed-Infectious-Recovered model. Simulation results are used to estimate vaccine efficacy ($\widehat{VE}$) with a Cox proportional hazards model.

Results: We find downward bias in $\widehat{VE}$ associated with low connectivity between communities in the study population and high force of infection, even when all participants in the trial are exchangeable at the time of randomization. This phenomenon arises because the stochastic dynamics in such a setting randomly lead to community-level variation in the force of infection. Stratifying a Cox model by community alleviates this bias with no loss of power.

Conclusion: Understanding and accounting for the impact of heterogeneous hazard rates can allow for more accurate estimates of $\widehat{VE}$ in epidemic settings.

Key words: vaccine trial, heterogeneous hazards, frailty, infectious disease, epidemics

Background/Aims

Network structure and individuals' degree of exposure to a pathogen can affect the efficacy analysis of interventions against infectious diseases. The "frailty" phenomenon, whereby heterogeneity in infection risk can cause randomized groups to increasingly differ as a trial progresses and more high-risk individuals become infected, has been well documented.[1,2,3] Using a time-weighted hazard-ratio analysis, such as a Cox model, when heterogeneity in infection risk exists can induce bias in the vaccine efficacy estimate ($\widehat{VE}$) relative to the true direct vaccine efficacy (VE).[4] The heterogeneity often occurs when a group of individuals has a higher risk of exposure compared to others *a priori*.[3,5] Through simulation, we characterize the magnitude and direction of the bias of $\widehat{VE}$ induced by heterogeneity of hazard rates in an individually randomized controlled trial of a leaky vaccine in which all participants are exchangeable at the beginning of the trial. We show that heterogeneous risk of infection arises due to the stochastic nature of epidemic dynamics in small populations, which leads individuals in some communities to experience higher infection risk than others. We then show that stratifying the analysis by community removes this bias without loss of power.

Methods

We model a vaccine trial by first generating a network of individuals grouped into communities, which are connected to a larger main population. Community size is uniformly distributed on a given range, with the mean community size and range as model inputs (Table 1). The average

number of connections individuals have with individuals in their own community and the average number of connections individuals have to those in other communities are each additional inputs of the model. Therefore, while individuals in the communities are not identical in terms of their exact number of connections, they are exchangeable in expected degree.

We then simulate a deterministic epidemic in the main population with a time-varying transmission rate, and stochastic epidemics in each of the communities. The disease natural history follows a Susceptible-Exposed-Infectious-Recovered model. A connection between two people represents a daily contact between them, meaning all susceptible individuals have a daily probability of infection from each of their infectious neighbors of $1-e^{-\beta}$, where ß is the force of infection for that contact. Additionally, each individual experiences a daily external hazard of infection from the main population, which varies with the prevalence of infection in the main population (Table 1).

7.5% of the population in the communities is enrolled into the trial, and individuals are randomized to either the vaccine or control groups. The vaccine is leaky, meaning that it reduces the probability of infection upon each exposure to an infectious individual;[6,7] for those vaccinated, the daily probability of infection from their infectious contacts is $1-e^{-\beta(1-VE)}$ where VE represents the direct leaky multiplicative vaccine efficacy input into the model. We estimate $\widehat{VE}$ with a Cox proportional hazards model for time to symptom onset, with trial status (i.e. vaccine or control) as the explanatory variable. Individuals who are never infected are censored at the end of the study period. We estimate $\widehat{VE}$ both unstratified and stratified by community. Power is estimated by the proportion of simulations in which the p-value associated with the estimated $\widehat{VE}$ is less than 0.05 and $\widehat{VE} > 0$.

We also estimate $\widehat{VE}$ from simulations of a trial of a vaccine with all-or-nothing effects, meaning it protects a certain percentage of people completely and others not at all, as well as from simulations varying different parameters, such as VE, the size of the communities, and the percent of each community enrolled into the trial. Additionally, we estimate $\widehat{VE}$ within subsets of the trial population, as subset analyses are often done, for example, within age groups or by sex.

Results

Using an unstratified Cox proportional hazards model to estimate $\widehat{VE}$ returns a downward bias in $\widehat{VE}$ relative to the input direct VE. As shown in Figure 1A, when input VE is set to 0.6, $\widehat{VE}$ from the unstratified analysis is less than 0.6. The bias increases with increases in R_0 and decreases as communities become more connected to each other. A Cox model stratified by community alleviates the bias without reducing power (Figure 1B). This bias does not occur when the input VE is set to 1 or 0 (see Fig. S1 and Fig. S2). As expected, this bias also does not occur in a risk-based analysis of a vaccine with all-or-nothing effects (see Fig. S3); however, a rate-based analysis of a vaccine with all-or-nothing effects returns an upward bias in $\widehat{VE}$ relative to the input direct VE (see Fig. S4).[6,7,8]

We find that heterogeneity in hazard rates in an individually randomized vaccine trial with a leaky vaccine leads to a downward bias of $\widehat{VE}$ even when all individuals are exchangeable at the start of the trial. Although the simulated network structure does not assign anyone to be high risk *a priori* (i.e. everyone has the same initial risk of infection), heterogeneity in exposure still arises. Given the stochastic nature of epidemic dynamics, which includes introductions into the

trial population from the larger main population, certain communities have larger outbreaks while others escape infection entirely. Individuals in a community with a large outbreak experience more exposure to infection than those in which there is not a large outbreak. This heterogeneity in hazard is well known to create a downward bias in $\widehat{VE}$[2,6,7] because the individuals at greater risk of infection (here, the individuals in communities with larger epidemics) are depleted more rapidly from the control group than individuals at less risk of infection, making the average hazard in the control group more similar to that in the vaccine group over the course of the trial. When R_0 is higher, individuals in communities with large outbreaks are exposed at an even higher rate than at lower levels of R_0, further exacerbating these effects. As communities become more connected, the heterogeneity in exposure between communities decreases because large outbreaks spill over into neighboring communities, alleviating some of the bias.

It is possible to show the source of the bias from the unstratified analysis in a causal directed acyclic graph (Figure 2). Let A be an indicator for vaccination status at baseline, $Y_{t=1}$ an indicator for infection at an early time point, and $Y_{t=2}$ be an indicator for infection at a second time point. Hazard ratio estimation at time = 2 conditions on those who were not infected at time = 1 ($Y_{t=1} = 0$), and the Cox model uses a weighted average of the time-specific hazard ratios.[4] Conditioning on $Y_{t=1}$ opens a backdoor path from A to $Y_{t=2}$, biasing the estimates of the effect of A on $Y_{t=2}$.[9] As shown in Figure 1A, the bias induced by heterogeneity in hazard rates across communities can be reduced by adjusting for community in a stratified Cox model analysis. This is because the backdoor path is blocked by conditioning on community.

We might expect the unstratified estimate to be biased due to a violation of the Cox model's proportional hazards assumption. To evaluate this hypothesis, we conducted a weighted residuals test for violation of proportional hazards of the unstratified analysis,[10] and then assessed the correlation between the resulting p-value and the difference between the stratified and unstratified $\widehat{VE}$. This test did not provide a clear indication of bias in the unstratified estimate (correlation = 0.02, p-value = 0.80) and thus should not be used to determine if stratification is necessary to obtain an unbiased estimate. In settings with fairly disconnected communities where there is potential for heterogeneity in hazard rates, we recommend conducting a stratified analysis. Although an individual frailty model could also alleviate the downward bias, stratification alleviates the bias without reducing power discernibly for the baseline assumptions considered here. However, when the sample size is very small, for example in the case of a subset analysis, stratifying to reduce bias leads to a loss of power (see Fig. S5).

Defining "community" for the purpose of stratification may present a challenge. While incorporating network structure into the design and analysis of trials is more often discussed in the context of cluster randomized trials, network surveys could also be used to identify the best unit for stratification in individually randomized trials.[11] However, as shown in Figure 1, the downward bias of the unstratified analysis is noticeable only when the percentage of connections outside an individual's community is less than 20%. In such a disconnected network, the communities will likely be distinct enough to identify, whereas in settings in which defining a community becomes more challenging, stratification will likely be unnecessary.

Further analysis indicates that the bias is not dependent on the size of the communities or the number of people from each community enrolled into the trial. An analysis with larger

communities and a ten-fold increase in the number of people from each community enrolled into the trial also results in a downward bias in VE estimate, which is alleviated by stratification (see Fig. S6).

Conclusion

It is well known that heterogeneity leads to a bias in $\widehat{VE}$.[3,5] However, it has previously only been discussed in the context of risk factor heterogeneity, either measured or unmeasured. Here we show that this bias can arise, and be alleviated, even when *a priori* heterogeneity does not exist. While these findings are specific to settings with fairly disconnected communities, understanding the potential sources of bias in analysis of vaccine trial results is essential for ensuring accurate estimates of $\widehat{VE}$, which are important for the design of both vaccine trials and vaccine programs. Two vaccines that are equally efficacious may appear to have different $\widehat{VE}$ if tested in different settings and analyzed without stratification, resulting in false conclusions about their relative efficacy. Furthermore, because $\widehat{VE}$ is required for calculating the vaccine coverage needed in order to achieve herd immunity in a population, an underestimate could lead to unnecessarily expensive vaccination campaigns.

Downward bias in the efficacy estimate for a leaky vaccine can occur in a population with a mixing structure other than complete random mixing, even when all trial participants are exchangeable *a priori*. Stratification by community, in a setting where mixing within communities is random, completely solves the problem with no loss of power. Stratified Cox models have previously been used in the analysis of vaccine efficacy studies, such as the

RTS,S/AS01 Malaria Vaccine individually randomized controlled trial, which stratified by study site.[12] However, such stratification is not a universal practice and was not used in recent analyses of dengue or cholera vaccine trials.[13,14] Stratification should be considered for future vaccine trials conducted in a large number of relatively disconnected centers, such as the planned Zika vaccine trials.

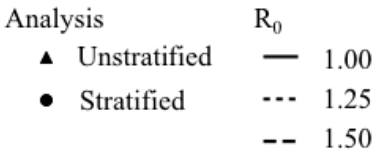
Acknowledgments

We thank Justin O'Hagan for helpful comments.

Declaration of conflicting interests

ML has performed consulting work related to vaccines for Merck, Pfizer, Affinivax and Antigen Discovery. He has received support for research through Harvard T.H. Chan School of Public Health from PATH Vaccine Solutions and Merck.

Figure 1. Unstratified vs stratified analyses: vaccine efficacy and power



Caption: Figure 1A shows the vaccine efficacy estimates using stratified and unstratified analyses as the percentage of connections an individual has outside of their community and R_0 vary (compared to known vaccine efficacy of 0.60). Variance of the estimates range from 0.005-0.162 for unstratified analyses and from 0.006-0.166 for stratified analyses, with lower variance for higher R_o. Figure 1B shows that the stratified analysis does not reduce power compared to the unstratified analysis.

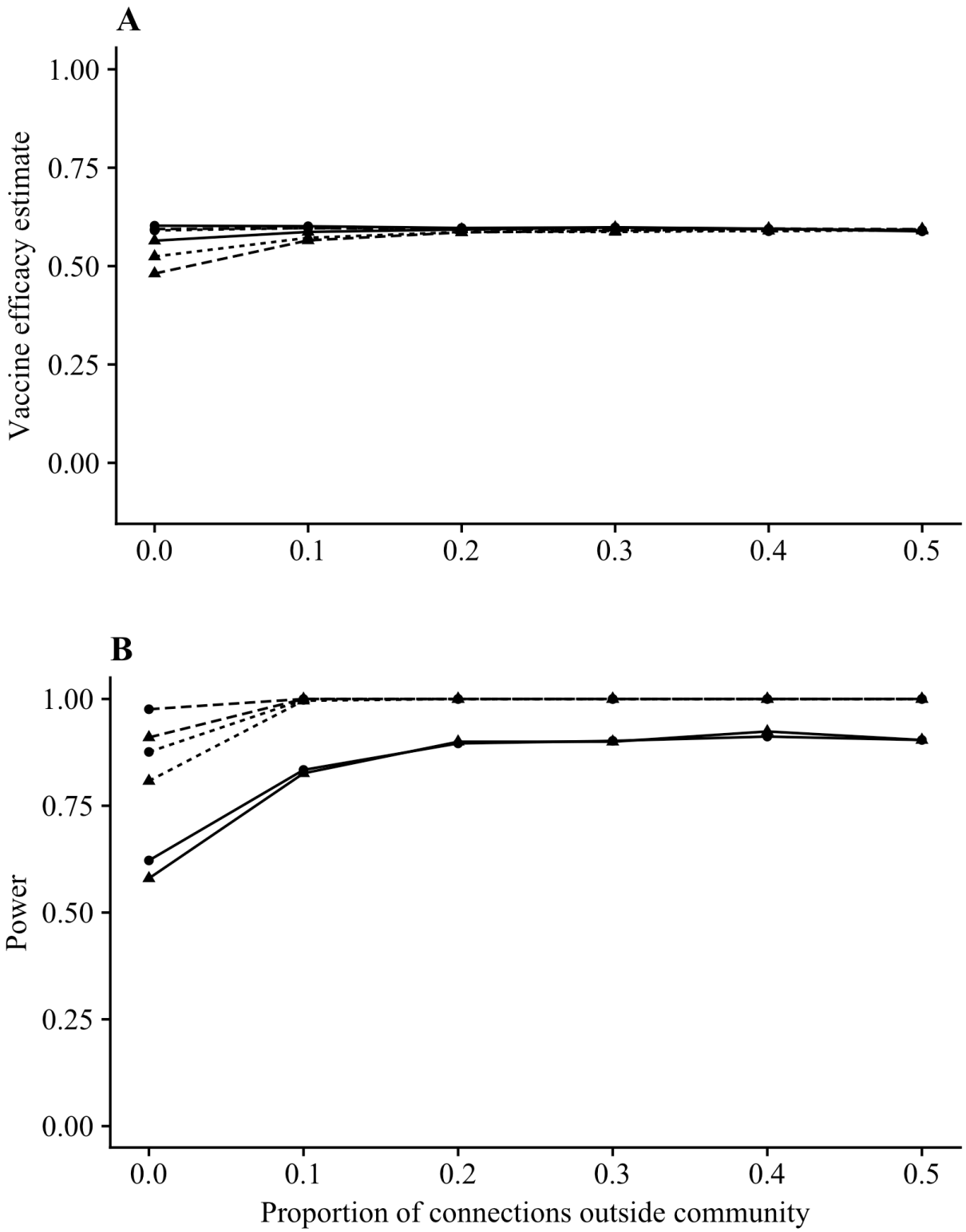

A
1.00
0.75
0.50
0.25
0.00
Vaccine efficacy estimate
0.0
0.1
0.2
0.3
0.4
0.5
B
1.00
0.75
0.50
0.25
0.00
Power
0.0
0.1
0.2
0.3
0.4
0.5
Proportion of connections outside community

Figure 2. **Causal directed acyclic graph of bias in unstratified analysis**

Caption: Figure 2 shows the source of the bias in the unstratified analysis. Conditioning on those who were not infected at time = 1 in the analysis at time = 2 opens a backdoor path between A (vaccination status) and $Y_{t=2}$ (outcome at time = 2), inducing bias.[9] *The dashed arrows indicate uncertainty regarding the relationship between A and Y, or the vaccine efficacy, which the trial aims to estimate. Note, only two times shown for simplicity.*

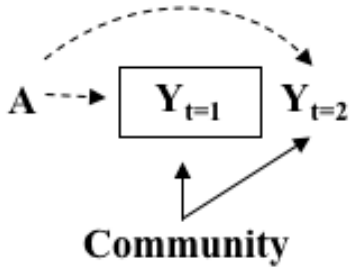

A
$Y_{t=1}$
$Y_{t=2}$
Community

Table 1. Parameters

Parameter	Meaning	Value/range
R_0	Average number of secondary infections generated by an infected individual within the communities; function of force of infection (ß), infectious period and network structure (Appendix 1)	1.00-1.50
Latent period	Latent period length (days)	9.7[15]
Mean (infectious)	Mean infectious period length (days); gamma distributed with rate = 0.226 and shape = 1.13	5.0[15]
VE	Individual vaccine efficacy	0, 0.6, 1
N_i	Size of community *i*	100 (range 80-120)
Num_ communities	Number of communities in the network	200
a	Constant in calculation of importation rate into communities from main population • $M_i = a * \sqrt{N_i}$ where M_i is importation rate and N_i is the size of community *i*[16] (Appendix 2)	0.025
Within degree	Average within-community degree[17]	7.5 – 15
Between degree	Average between-community degree[17]	0 – 7.5
Trial size	Average number of individuals enrolled	1,500
Trial start day	First day of enrollment, vaccination and start of follow-up, relative to the first day of the epidemic in the main population	150

Trial length	Length of follow-up after trial start (days)	140

Appendix 1. R_0 calculation[18]

$$R_0 = T^*(\frac{\langle k^2 \rangle}{k} - 1)$$

$$T = 1 - (\frac{\gamma}{\gamma + ß})^{\alpha}$$

k = mean degree of the network

k^2 = mean square degree of the network

γ = infectious period rate

α = infectious period shape

ß = force of infection

Appendix 2. Connection between main population and communities

F_i*I = daily hazard of infection for an individual in community *i* from the main population

where:

- F_i = proportionality constant for the degree of contact between the main population and community *i*, with higher importation rate (M) for larger communities
- I = number of infectious individuals in main population

References

1. Longini IM, Elizabeth Halloran M. A Frailty Mixture Model for Estimating Vaccine Efficacy. *Appl Stat* 1996; 45: 165.

2. Halloran ME, Longini IM Jr, Struchiner CJ. Estimability and interpretation of vaccine efficacy using frailty mixing models. *Am J Epidemiol* 1996; 144: 83–97.

3. Halloran ME, Elizabeth Halloran M, Haber M, et al. Interpretation and Estimation of Vaccine Efficacy under Heterogeneity. *Am J Epidemiol* 1992; 136: 328–343.

4. O'Hagan JJ, Lipsitch M, Hernán MA. Estimating the per-exposure effect of infectious disease interventions. *Epidemiology* 2014; 25: 134–138.

5. Edlefsen PT. Leaky Vaccines Protect Highly Exposed Recipients at a Lower Rate: Implications for Vaccine Efficacy Estimation and Sieve Analysis. *Comput Math Methods Med* 2014; 2014: 1–12.

6. Smith PG, Rodrigues LC, Fine PE. Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *Int J Epidemiol* 1984; 13: 87–93.

7. Halloran ME, Haber M, Longini IM Jr, et al. Direct and indirect effects in vaccine efficacy and effectiveness. *Am J Epidemiol* 1991; 133: 323–331.

8. White MT, Griffin JT, Drakeley CJ, et al. Heterogeneity in malaria exposure and vaccine response: implications for the interpretation of vaccine efficacy trials. *Malar J* 2010; 9: 82.

9. Greenland S, Pearl J, Robins JM. Causal Diagrams for Epidemiologic Research. *Epidemiology* 1999; 10: 37–48.

10. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; 81: 515–526.

11. Staples PC, Ogburn EL, Onnela J-P. Incorporating Contact Network Structure in Cluster Randomized Trials. *Sci Rep* 2015; 5: 17581.

12. Neafsey DE, Juraska M, Bedford T, et al. Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine. *N Engl J Med* 2015; 373: 2025–2037.

13. Qadri F, Wierzba TF, Ali M, et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *N Engl J Med* 2016; 374: 1723–1732.

14. Hadinegoro SR, Arredondo-García JL, Capeding MR, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med* 2015; 373: 1195–1206.

15. WHO Ebola Response Team, Aylward B, Barboza P, et al. Ebola virus disease in West Africa--the first 9 months of the epidemic and forward projections. *N Engl J Med* 2014; 371: 1481–1495.

16. Keeling MJ, Rohani P. *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press, 2007.

17. Faust K, Wasserman S. Blockmodels: Interpretation and evaluation. *Soc Networks* 1992; 14: 5–61.

18. Meyers LA, Pourbohloul B, Newman MEJ, et al. Network theory and SARS: predicting outbreak diversity. *J Theor Biol* 2005; 232: 71–81.